REMARKS

In the Office Action mailed May 8, 2008, claims 10, 43-49, 51, 115, 117, 119, and 120-135 were rejected under 35 USC §112, second paragraph for allegedly being indefinite.

Claims 1-8, 10, 43, 44, and 51 were rejected for allegedly being anticipated under 35 USC §102(b) by Hortin.

Claims 1, 6-8, 10, 43-49, 51, and 112-135 were rejected for allegedly being obvious based upon Hortin in view of Pittman et al.; Bakker et al.; and Ramabhadran.

Applicant would like to thank the Examiner for the careful consideration given the present application. The application has been carefully reviewed in light of the Office action, and amended as necessary to more clearly and particularly describe the subject matter which Applicant regards as the invention.

Claims 1-8, 10, 43-49, 51, and 112-135 remain pending and are presented for the Examiner's further consideration.

A. Rejection Under §112 Should be Withdrawn

In this first review by the US Patent and Trademark Office, claims 10, 43-49, 51, 115, 117, 119 and 120-135 were rejected under 35 USC § 112, second paragraph for allegedly being indefinite. The grounds for this rejection are set forth on pages 2-3 of the noted Office action. Each ground is addressed as follows.

1. The Terms "Peptide Analogues" and "Mimic" Are Sufficiently Definite

Specifically, regarding claims 10, 51, 115, 119, 127, and 135, concern was expressed over the terms "peptide analogues" that "mimic" various peptides. Specifically, the Office questioned the nature and degree of such mimicry, and whether the claims require particular structures, functions, effects on cells or patients, or some combination thereof.

These claims refer to a compound, i.e. a peptide analogue, that mimics the critical features of the molecular recognition process of a peptide of interest and thereby blocks or reproduces the action of the peptide. Additional description and examples of these terms are provided on page 17, lines 7-21 of the present application:

> The present discovery also includes the use of peptide analogue(s) in place of, or in addition to, the peptides described herein. A peptide analogue as referred to herein refers to a compound that is capable of mimicking or antagonizing the biological action(s) of a parent or natural peptide. An example of a peptide analogue is a peptidomimetic. Generally, a peptide analogue as used herein is a compound that mimics the critical features of the molecular recognition process of the parent peptide and thereby blocks or reproduces the action of the peptides. An example of a non-peptide peptidomimetic agonist for a peptide receptor system is morphine, which mimics the opioid peptides. A peptide analogue can also include any of the previously noted non-naturally occurring peptides, stereoisomers, peptides containing one or more non-hydrolysable bonds between adjacent amino acids, constrained peptides, or equivalents thereof. Similarly, each of the sequence identifiers noted herein include and encompass conservatively modified variants thereof.

Thus, according to the specification of the present application, the term "peptide analogue" refers to a compound that is capable of mimicking or antagonizing the biological action(s) of a parent or natural peptide. The term is further defined by noting that generally, such peptide analogues mimic the critical features of the molecular recognition process of the parent peptide and thereby block or reproduce the action of the peptide. In view of this definition, the recited

peptide analogues in the claims at issue do in fact have structures, functions, effects on cells or patients, or some combination thereof, similar to the peptide of interest. The nature and degree to which the peptide analogues mimic the referenced peptide is described in the previously quoted passage from the specification. That is, the nature or degree of the mimicking is such that the peptide analogue imitates the peptide of interest, or produces an effect as would the peptide of interest.

It is respectfully submitted that the Office will also appreciate that these terms are well understood by those skilled in this field of art. And, particularly, these terms would be understood by those skilled in the art when read in light of the specification. And therefore, the claims at issue are sufficiently definite and meet the requirements of §112, second paragraph. "Patents...are written to enable those skilled in the art to practice the invention, not the public." W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983) cert denied, 469 US 851 (1984). "A decision as to whether a claim is invalid under this provision [§112, second paragraph] requires a determination whether those skilled in the art would understand what is claimed." Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991), cert denied, 502 US 856 (1991). "Whether a claim is invalid for indefiniteness requires a determination whether those skilled in the art would understand what is claimed when the claim is read in light of the specification." Morton International, Inc. v. Cardinal Chemical Co., 5 F.3d 1464, 28 USPQ2d 1190 (Fed. Cir. 1993), on remand from, 508 US 83, 26 USPQ2d 1721 (1993). "The operative standard for determining whether this requirement has been met is 'whether those skilled in the art would understand what is claimed when the claim is read in light of the specification.'" Beachcombers, Int.,

Inc. v. Wildewood Creative Products, Inc., 31 F.3d 1154, 31 USPQ2d 1653 (Fed. Cir. 1994).

In view of the foregoing, it is respectfully submitted that the Office will appreciate that the claims at issue, namely claims 10, 51, 115, 119, 127 and 135, when read in light of the specification by a person skilled in this field of art, would be understood, and thus these claims meet the requirements of 35 USC §112, second paragraph.

2. The Term "Adapted for Inhibiting Thrombin Generation" is Sufficiently Definite

Concern was expressed over claims 43, 120, and 128 for their recitation for a composition "adapted for inhibiting thrombin generation."[1] Specifically, the Office asserted that clarification was required since "it is not clear what physical properties of the composition render it particularly adapted for this function."

It is respectfully requested that the Office identify the requirement that patent claims for a composition must identify physical properties of the composition that render the composition adapted for a particular function recited in the claim. Neither Applicant nor Applicant's attorneys are aware of any such requirement in the law. Instead, it is respectfully submitted that these claims at issue are in fact sufficiently definite and meet the standard for §112, second paragraph because these claims would be understood by a person skilled in this field of art, and particularly, when read in view of the specification.

1 Since claims 44-49 and 51 depend (or ultimately depend) from claim 43, these claims were also rejected on the grounds noted for claim 43. Similarly, since claims 121-127 and 129-135 depend (or ultimately depend) from claims 120 and 128, these claims were also rejected on the grounds noted for claims 120 and 128.

Regarding the Office's concern that the source or location of thrombin referenced in claims 43, 120, and 128 must be identified, this is also believed to not be necessary. Again, it is respectfully requested that the Office identify the requirement that patent claims directed to a composition for undertaking some function with regard to another agent, must recite the location or source of that agent. It is believed that limiting claims 43, 120 and 128 to thrombin at a specific location or from a specific source is not required. The prior art of record, it is respectfully submitted, does not require any of these claims to be limited in this regard.

In summary, the term at issue, i.e. "adapted for inhibiting thrombin generation" refers to characteristics of the claimed composition which cause or otherwise result in thrombin generation to be inhibited. Thrombin, as known by those skilled in this field of art, is a coagulation protein existing in many biological systems, most notably humans. However, the claims at issue are not limited to inhibiting the generation of thrombin in humans or from humans. Again, it is submitted that the cited art does not require such.

3. Use of Transitional Phrases Clarified

Claim 117 has been clarified in accordance with the helpful suggestions from the Examiner. It is believed that this ground of rejection has been remedied.

In view of the foregoing explanations and clarifications, it is respectfully submitted that the present rejection of claims under §112, second paragraph has been remedied and should be withdrawn.

It is respectfully submitted that each of claims 10, 43-49, 51, 115, 117, 119, and 120-135, are sufficiently definite and satisfy the requirements of 35 USC §112, second paragraph.

B. Rejection Under §102 Should be Withdrawn

The Office rejected claims 1-8, 10, 43, 44, and 51 under 35 USC § 102(b) for allegedly being anticipated, i.e. identically disclosed, by a previously cited 1990 article to Hortin.[2]

As described in the specification of the present application, the present invention relates to the discovery of specific peptides, typically consisting of four or five amino acids, that have been found to significantly inhibit the generation of thrombin and thus serve as anticoagulants. These particular peptides include those containing the amino acid sequence DYDY, DYDYQ, and the sulfonated sequences of DYDY and DYDYQ, in which at least one of the Y amino acids is sulfonated.

Of the rejected claims 1-8, 10, 43, 44, and 51; claims 1 and 43 are independent claims. Claims 1-7 recite a peptide having a sequence of amino acids which is identical to a sequence of consecutive amino acids found within amino acids 695 to 698 (SEQ ID NO. 10) of the human blood clotting factor Va.[3] Claim 8 is for a pharmaceutical composition comprising the peptide of claim 1. Claim 10 recites a peptide analogue that mimics the peptide of claim 1. Independent claim 43 recites a pharmaceutical composition adapted for inhibiting thrombin generation, the composition comprising a peptide that includes an amino acid sequence DYDY.

---

[2] Hortin, G.L., "Sulfation of Tyrosine Residues in Coagulation Factor V," Blood, 1 September 1990, Vol. 76 No. 5, pages 946-952.

[3] SEQ ID NO. 10 corresponds to the amino acid sequence DYDY.

And, claim 51 recites a pharmaceutical composition that comprises a peptide analogue that mimics the peptide of claim 43.

Before turning attention to the present rejection, it is instructive to review the legal standard for properly rejecting claims under §102. "For a prior art reference to anticipate in terms of 35 USC §102, every element of the claimed invention must be identically shown in a single reference... These elements must be arranged as in the claim under review." In re Bond, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990). "Anticipation under Section 102 can be found only if a reference shows exactly what is claimed." Titanium Metals Corp. v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985).

In rejecting the claims at issue, the Office asserted that:

> The claims are interpreted as being drawn to a peptide comprising a sequence of amino acids that is identical to a sequence of at least 2 consecutive amino acids found within a 4-amino acid region of a longer reference sequence. In some dependent claims, the peptide has a particular activity or comprises a particular sequence. Some claims are drawn to compositions comprising the peptide or compounds that mimic the peptide in some way. It is noted for the record that claim 1 is currently so broad as to encompass any peptide that contains either the sequence DY or the sequence YD along with any other amino acids in any sequence. The scope of claim 43 encompasses any peptide that contains the sequence DYDY along with any other amino acids in any sequence.

Pages 3-4 of the Office Action mailed May 8, 2008.

It is respectfully submitted that an overly broad interpretation is being given to term "peptide" in the claims at issue. Instead, the term "peptide" as used in the claims and by those skilled in the art, generally refers to a relatively short chain of amino acids, such as from about 2 to about 10 amino acids, and at most up to about 50 amino acids.

Apparently, under the overly broad interpretation of the term "peptide," the Office reads the claims as encompassing the disclosure by Hortin, and in particular, the mention of Factor V by Hortin:

> Hortin teaches that the complete sequence of human coagulation factor V (hereafter "Factor V") was known at the time of the invention and that said sequence includes the sequence DYDYQ (page 946, column 1, paragraph 2; and Figure 6 at page 950, e.g.). Hortin teaches a solution comprising Factor V (page 946, column 2, last paragraph).

Page 4 of the Office Action.

No. Factor V as disclosed in the Hortin article is a protein, and includes about 2200 amino acids. Practitioners in the field of biochemistry refer to Factor V as a protein and not as a peptide. Restated, Factor V is not considered a peptide, and so is excluded by each of the claims at issue, i.e., claims 1-8, 10, 43, 44, and 51, since each of those claims expressly recites a "peptide." Had Applicant intended to claim Factor V or proteins, Applicant would have used the word "protein" in the claims and not expressly limited the claims to peptides.

In support of the rejection under §102, the Office argued that the claimed products and the prior art products are "identical," "substantially identical," or "the same":

> M.P.E.P. §2112 recites, "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established." *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).
>
> * * *
>
> In this case, the claims encompass numerous peptides, including Factor V itself. Peptides cannot be separated from their inherent properties, and since the peptide as instantly claimed is identical in structure to the prior art peptide, the two necessarily have the same properties, including those recited in claims 2-5 and 43. Claims 10 and 51 are included in this rejection because a given composition is a perfect mimic of itself in every way.

Pages 4-5 of the Office Action.

In no way is Factor V disclosed by Hortin, identical to, substantially identical to, nor the same, as the peptides recited in claims 1-8, 10, 43, 44, and 51. As previously explained, Factor V is a protein and includes about 2200 amino acids. The claims at issue specifically recite peptides, which are relatively short chains of amino acids, such as from about 2 to about 10 amino acids, and at most up to about 50 amino acids. Factor V is not identical to the claimed peptides.

The article by Hortin, representing the state of the art from nearly twenty (20) years ago, also describes several fragments of Factor V. One of the fragments is the well known Factor Va. Hortin speculates a region of Factor Va, using a predictive algorithm, as depicted in Figure 6.

Hortin entirely fails to disclose the peptide of independent claim 1. As noted, claim 1 recites a peptide having a sequence of amino acids identical to the sequence of consecutive amino acids 695 to 698 of Factor Va. Hortin discloses Factor Va, and at best, only discloses a speculated region within the 105,000 dalton fragment Va of Factor V. Hortin does not disclose a peptide having the recited sequence of amino acids contained within a complex molecule of about 2200 amino acids. Anticipation of a claimed peptide does not occur by merely pointing to various amino acids in a complex protein. Nor does anticipation of the peptides in the claims at issue occur by pointing to amino acid sequence 695 to 698 in Factor Va speculatively shown by Hortin. Claim 1 does not recite nor include Factor Va. Applicant is not claiming Factor Va. Instead, claim 1 recites a peptide having a specific amino acid sequence. Simply put, Hortin only discloses, and more

accurately, only speculates as to the identity of a region of Factor Va. Simply put, Hortin does not disclose a peptide containing the sequence of interest.

In the rejection of claims under §103 (which is addressed later herein), the Office combines the article to Hortin with several other references due to Hortin's admitted failure to disclose certain claimed features. In this regard, *the Office recognized that Hortin does not disclose the claimed peptides:* "Hortin does not exemplify a peptide in which one or both of the tyrosines in the DYDY or DYDYQ motif are sulfated. Hortin does not teach any fragments of Factor V, e.g. the tetrapeptide DYDY or the pentapeptide DYDYQ." Page 6 of the Office Action. Thus, the Office recognizes and admits that Hortin fails to disclose the peptides DYDY and DYDYQ.

Similarly, it will be appreciated that independent claim 43 is not anticipated by Hortin. Independent claim 43 recites in part, a pharmaceutical composition including a peptide having an amino acid sequence DYDY. As previously explained, Hortin merely discloses Factor Va and at best, speculates as to a region of amino acids within that factor. Hortin fails to disclose a peptide having the claimed sequence of interest, and entirely fails to disclose a pharmaceutical composition that includes the claimed peptide.

Since independent claims 1 and 43 are not anticipated by Hortin, neither are any of claims 2-8, 10, 44, and 51 which are dependent or ultimately dependent from these independent claims and thus contain all of the recitations from their respective independent claim.

Furthermore, Hortin entirely fails to identify any specific sequence of amino acids in any region of Factor Va that are responsible for inhibiting the generation of

thrombin. Furthermore, Hortin entirely fails to disclose that if any particular peptide or sequence of amino acids from any region of Factor Va were isolated, that the peptide or amino acid sequence would exhibit the anticoagulant effects of the present invention.

Additionally, many of the claims at issue recite specific features that are clearly not disclosed by Hortin. For example, dependent claims 2-5 recite peptides of claim 1 that exhibit various IC_{50} values. Where in the article to Hortin are these peptides disclosed? Where are any references to activity levels by peptides disclosed in the article to Hortin? It is respectfully submitted that upon further review, the Office will appreciate this in furtherance of the withdrawal of the rejection of these claims.

For at least these reasons and in summary, it is respectfully submitted that the article to Hortin fails to anticipate, i.e. identically disclose, any of claims 1-8, 10, 43, 44, and 51.

C. Rejection Under §103

The Office rejected claims 1, 6-8, 10, 43-49, 51, and 112-135 under 35 USC § 103(a) for allegedly being obvious based upon the article to Hortin, in view of articles to Pittman et al., Bakker et al., and Ramabhadran.[4]

Before addressing the specific arguments presented by the Office, it is instructive to consider in greater detail each of the cited articles that were combined with Hortin.

[4] On page 5 of the Office action, the action states "[t]his application currently names joint inventors..." It is believed that inclusion of this statement in the action is a typographical error. The present application names a single inventor, Michael Kalafatis.

1. Pittman et al.

Pittman et al.,[5] representing the state of the art from fifteen (15) years ago, note that Factor V is a cofactor in the blood coagulation cascade. Pittman et al. note that Factor V requires activation by thrombin for functional activity. Pittman et al. continue and describe sulfation of Factor V and that such sulfation affects the rate of activation by thrombin: "[S]ulfation of factor V is required for rapid cleavage by thrombin" p. 6956.

2. Bakker et al.

Bakker et al.,[6] also from fifteen (15) years ago, describe functional properties of Factor Va, by investigating a modified form of this factor lacking a certain range of amino acids. An enzyme from certain snake venom was identified as converting Factor Va into a molecule having greatly reduced cofactor activity. The authors concluded that the loss of a 27-amino acid peptide from Factor Va impaired interaction between the treated Factor Va with prothrombin and a cofactor.

3. Ramabhadran

Ramabhadran,[7] also from about fifteen (15) years ago, describes that peptides can be chemically synthesized.

---

[5] Pittman, D.D., et al., "Posttranslational sulfation of factor V is required for efficient thrombin cleavage and activation and for full procoagulant activity," Biochemistry, Vol. 33, No. 22, pp. 6952-6959, 1994.

[6] Bakker HM et al. 1994. Functional properties of human Factor Va lacking the Asp683-Arg709 domain of the heavy chain. J Biol Chem 269: 20662-20667

[7] Ramabhadran TV. 1994. Pharmaceutical Design and Development: A Molecular Biology Approach. Ellis Horwood, Hertfordshire UK. Pages 40, 42, and 43.

The Office then combines these four references, i.e. Hortin, Pittman et al., Bakker et al., and Ramabhadran to conclude that claims 1, 6-8, 10, 43-49, 51, and 112-135 are obvious:

> A person of ordinary skill in the art would have had a reasonable expectation of success in sulfating either or both of the tyrosine residues at positions 696 and 698 within Factor V because Hortin and Pittman both teach that these residues are within consensus sequences for sulfation. The skilled artisan would have been motivated to sulfate one or both of these residues in Factor V because Pittman teaches that Factor V is not active unless it is sulfated.
>
> The person of ordinary skill in the art would have had a further reasonable expectation of success in producing short peptides including tyrosine residues 696 and 698 because Hortin teaches that the entire sequence of Factor V was known at the time of the invention and because Ramabhadran teaches that peptides of up to 50 amino acids in length and with a given sequence may be chemically synthesized. The skilled artisan would have been motivated to produce such peptides because Bakker teaches that the C-terminal portion of Factor V heavy chain, which comprises tyrosine residues 696 and 698, is the domain required to bind prothrombin; the skilled artisan would have been motivated to determine which of these 27 residues is necessary for the interaction and which are not. Furthermore, sulfating these residues would have constituted routine experimentation on the part of the skilled artisan, since Pittman teaches methods for doing so. The skilled artisan would have been motivated to sulfate the tyrosine residues because Pittman and Horton both teach that they may be sulfated *in vivo*, because Bakker teaches that these residues are within a domain that binds prothrombin, and because Pittman teaches that Factor V must be sulfated to bind thrombin. Therefore, the skilled artisan would have endeavored to learn whether the tyrosine residues in the 27-amino acid peptide of Bakker need to be sulfated to bind prothrombin. In light of the practical teachings and predictions of the art, the selection of the peptide sequence and sulfation pattern would have constituted routine experimentation at the time of the invention. See *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007).
>
> The skilled artisan would have had a reasonable expectation that peptides made as suggested by the art as set forth above would inhibit thrombin activity because Hortin teaches that Factor V is bound and cleaved by thrombin, Bakker teaches that the C-terminal 27 amino acids of Factor V are the portion involved in binding thrombin, and Pittman and Horton teach that residues 696 and 698 are likely required for thrombin binding. See KSR.
>
> It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to produce peptides using the method of Ramabhadran that correspond to various portions of the 27 amino acids of Factor V taught by Bakker to be involved in binding thrombin in order to determine which portions of this fragment are necessary for thrombin binding. It would have been further obvious to sulfate one or more of the tyrosine residues within the resulting peptide because Pittman teaches that sulfation is required for activity and teaches methods for sulfating proteins.
>
> Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Pages 7-9 of the Office Action.

It is respectfully submitted that several flaws exist in the purported combining of references and conclusions drawn therefrom. The Office argues in the above quoted passage that Hortin and Pittman teach that residues 696 and 698 "are likely required for thrombin binding" and that "these residues are within consensus sequences for sulfation." The Office then, without identifying any basis in the art, concludes that it would have been obvious to provide a peptide for inhibiting thrombin generation having a sequence of amino acids DYDY (claims 1, 112) or a sequence of amino acids DYDYQ (claim 116); or a pharmaceutical composition for inhibiting thrombin generation including a peptide having the sequence of amino acids DYDY (claims 43, 120) or a sequence of amino acids DYDYQ (claim 128).

As previously noted, the Office admitted that Hortin does not teach either of the peptides DYDY or DYDYQ. Pittman also fails to teach or suggest peptides having either of these specific sequences. Regarding the claimed sulfated peptides, the Office admitted that Hortin also fails to teach such. Pittman, at best, only suggests that sulfation affects the rate of activation by thrombin, and that sulfation of Factor V is required for rapid cleavage by thrombin.

It is respectfully submitted that in reaching the present conclusion of obviousness, the Office has unwittingly engaged in impermissible hindsight reconstruction. That is, without having the benefit of Applicant's claims which expressly identify the sequences DYDY and DYDYQ, the cited prior art would not lead a practitioner in this field to arrive at the claimed subject matter. "Care must be taken to avoid hindsight reconstruction by using 'the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit.'" Grain Processing Corp. v. American

Maize-Products Corp., 840 F.2d 902, 5 USPQ2d 1788 (Fed. Cir. 1988). "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). "Determination of obviousness can not be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention." ATD Corp. v. Lydall, Inc., 159 F.3d 534, 48 USPQ2d 1321 (Fed. Cir. 1998).

Apparently recognizing the "leap" made from the collection of prior art to the claimed subject matter, the Office fills in this extensive gap by asserting, "the selection of the peptide sequence and sulfation pattern would have constituted routine experimentation." In support of this, the Office cited KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385 (US 2007).

It is unclear why the Office now apparently asserts a new standard for obviousness rejections. By contending that the claimed subject matter was arrived at by "routine experimentation," the Office is apparently basing patentability upon the manner by which the invention was discovered. There is no such basis in the law for this. In point of fact, this is prohibited by statute: "Patentability shall not be negatived by the manner in which the invention was made." 35 USC §103(a).

It is acknowledged that the KSR decision now enables the Office and Examiners, when undertaking an obviousness analysis, to take account of the inferences and creative steps of a person having ordinary skill in the art, rather than having to identify precise teachings in the art directed to the specific subject matter of the claims.

However, it is respectfully urged that the subject matter of the claims at issue, exhibits unexpected and remarkable benefits and results, as described throughout the present application, and as particularly shown in Figs. 10-13 for example. These surprising and significant benefits and results indicate the nonobviousness of the claimed subject matter. Nowhere in any of the cited prior art is there any suggestion of these remarkable properties, e.g. the pronounced activity levels, inhibitory functions, and significantly altered clotting times achieved by the claimed subject matter.

The claimed subject matter goes significantly beyond any combination of known elements from the art that would merely produce predictable results.

Furthermore, it is significant that one of the references relied upon for the present rejection actually teaches away from the subject matter of the pending claims. Bakker et al. describe a modified Factor Va designated as Va_{NO} that is obtained by incubating Factor Va with an enzyme from the venom of *N. naja oxiana*. Bakker et al. describe several comparative tests in which the inhibitory modified Factor Va is compared to untreated Factor Va:

> With the factor Xa-Va complex the reaction was characterized by a Km for prothrombin of 0.24μM and a V_{max} of 6860 mol of prothrombin activated per min. per mol of factor Xa....In the case of the factor Xa-Va_{NO} complex the Km was less favorable (0.83 μM), whereas V_{max} was slightly higher (7685 mol of prothrombin activated per min. per mol of factor Xa).

P. 20665 of the article to Bakker et al. In addition, see Fig. 5 on p. 20666.

A person skilled in this field of art, desirous of identifying a strategy or agent for inhibiting thrombin generation, after considering the article to Bakker et al. would be motivated to investigate other amino acid regions in Factor Va besides those of the 27 amino acid section that were cleaved from the factor by the snake enzyme.

This is because *the modified Factor Va_{NO} causes greater prothrombin activation* as evidenced by a higher Km and faster V_{max} than unmodified Factor Va. Thus, this is why Bakker et al. conclude that, "[t]hus, the final 27 carboxyl-terminal residues of the factor Va...do not play a role in the increase of the k_{cat} of prothrombin activation."

No doubt the Office will appreciate that such a teaching away effectively rebuts the present rejection. "A prima facie case of obviousness can be rebutted if the applicant...can show 'that the art in any material respect taught away' from the claimed invention." In re Haruna, 249 F.3d 1327, 58 USPQ2d 1517 (Fed. Cir. 2001). "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." Tec Air, Inc. v. Denso Manufacturing Michigan Inc., 192 F.3d 1353, 52 USPQ2d 1294 (Fed. Cir. 1999).

In view of the foregoing, it is respectfully submitted that the Office will appreciate that the present obviousness rejection should be withdrawn.

D. Conclusion

In light of the foregoing, it is respectfully submitted that the present application is in a condition for allowance and notice to that effect is hereby requested. **If it is determined that the application is not in a condition for allowance, the Examiner is invited to initiate a telephone interview with the undersigned attorney to expedite prosecution of the present application.**

If there are any additional fees resulting from this communication, please charge same to our Deposit Account No. 18-0160, our Order No. CSU-17999.

Respectfully submitted,

RANKIN, HILL & CLARK LLP

By /Mark E. Bandy/
Mark E. Bandy, Reg. No. 35788

38210 Glenn Avenue
Willoughby, Ohio 44094-7808
(216) 566-9700